Chemotherapy in Patients ≥80 with Advanced Non-small Cell Lung Cancer: Combined Results from SWOG 0027 and LUN 6

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Introduction: We report outcomes for the combined cohort of patients ages 80 or older from two chemotherapy trials in advanced non-small cell lung cancer (NSCLC) conducted by the Southwest Oncology Group (S0027) and an investigator-initiated trial (LUN 6).
Methods: Patients with chemotherapy-naïve, stage IIIB/IV NSCLC, ages 70 years or older with a performance status (PS) of 0 or 1, or patients of any age with PS 2, were eligible. Treatment in the S0027 study was 25 mg/m^2 of vinorelbine on days 1 and 8, every 21 days for three cycles, and then 35 mg/m^2 of docetaxel on days 1, 8, and 15, every 28 days for three cycles. Treatment in the LUN 6 study was 30 mg/m^2 of docetaxel on days 1, 8, and 15, every 28 days, or 75 mg/m^2 every 21 days. Of the 228 patients treated, 49 (21.5%; 26 in LUN 6 and 23 in S0027) were ages 80 years or older. Analysis of outcome was conducted in the 80-and-older group and was compared with the under-80 cohort from S0027.
Results: Among patients with measurable disease, disease-control rates (partial response + stable disease) were 54% (n = 48) and 46% (n = 89) in the 80-and-older and under-80 groups, respectively. Median survival was 7 and 11 months in PS 0/1 patients in the 80-and-older and under-80 groups, respectively. Median survival was 4 and 5 months in PS 2 patients in the 80-and-older and under-80 groups, respectively. Treatment was well tolerated. Five treatment-related deaths were noted: two (4%) and three (3.4%) in the 80-or-younger and the under-80 groups, respectively.
Conclusions: These chemotherapy regimens were associated with an encouraging disease-control rate (54%) in patients 80 years or older with advanced NSCLC, with good tolerance. Selected octogenarians with advanced NSCLC may benefit from single-agent chemotherapy.

Key Words: Non-small cell lung cancer, Chemotherapy, Octogenarians.

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Lung cancer is the leading cause of cancer mortality in both men and women. It is projected that nearly 163,000 individuals will die from lung cancer in the United States in 2006.[1] Risk of lung cancer clearly increases with advancing age. Given the changing demographics of Western populations, the proportion of lung cancer patients older than 65 years has increased progressively in recent years. The latest data from the U.S. Surveillance, Epidemiology, and End Results program indicate that more than two of every three lung cancer patients are more than 65 years old.[2] In addition, the proportion of patients ages 75 years or older has increased to 35%, and the median age of newly diagnosed patients with lung cancer in the United States is now 70 years.[2]

Despite the high proportion of older patients with lung cancer, until relatively recently, there has been a paucity of information from clinical trials to guide patient management in this population. Analyses of trials sponsored by the National Cancer Institute have documented the disproportionately low representation of older patients in most disease sites, including lung cancer.[3,4] Retrospective analyses conducted on the subset of patients older than 70 years in a number of phase III trials in advanced non-small cell lung cancer (NSCLC) have suggested that platinum-based doublet therapy may be an appropriate option for fit elderly patients.[5–9] In addition, a number of elderly-specific prospective trials have clearly established the efficacy of single-agent

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chemotherapy in patients ages 70 years or older with advanced NSCLC.[10–12]

Despite the value of the emerging database on the use of chemotherapy in elderly patients with NSCLC, virtually no information is currently available to guide treatment decisions for the growing group of patients ages 80 years or older. This group of "very old" patients is rapidly growing in numbers, accounting for more than 20% of all deaths from lung cancer in the United States in 2006.[1] Given the absence of prospective data on the outcome of chemotherapy treatment in "very old" NSCLC patients, we conducted an analysis of treatment outcomes in patients ages 80 years or older from two trials conducted by the Southwest Oncology Group (S0027), and a multicenter investigator-initiated trial (LUN 6). Both trials had similar eligibility requirements (patients older than 70 years with advanced NSCLC and/or with a performance status [PS] of 2) and single-agent treatment regimens, which encouraged the inclusion of patients ages 80 years or older. Reports on the complete study populations from each of these studies have been reported previously.[13,14] This manuscript details treatment outcomes for the proportion of patients at least 80 years old compared with the cohort of patients under age 80 from S0027.

PATIENTS AND METHODS

Eligibility

Patients were required to have histologically or cytologically documented stage IIIB (LUN 6: any; S0027: pleural effusion only) or stage IV NSCLC. Patients ages 70 years or older with PS of 0/1, or those of any age with PS 2, were eligible. All patients were required to be 18 years of age or older and to have acceptable hepatic, cardiac, and hematologic function. Patients on S0027 were required to have measurable or evaluable disease documented by computed tomography, magnetic resonance imaging, x-ray, physical exam, or nuclear exam. Patients with brain metastases were excluded from S0027. They were allowed on LUN 6 if the brain metastases were controlled. No prior systemic chemotherapy, biologic therapy, or radiation therapy for NSCLC was allowed. Patients with symptomatic neuropathy of grade 2 or higher, or active pregnancy, were ineligible for inclusion in the trial. The study was approved by the institutional review boards of the respective institutions, and all patients gave written informed consent.

Treatment Plan

S0027

Patients received 25 mg/m^2 of vinorelbine intravenously on day 1 and day 8 of a 21-day cycle for three cycles, followed by 35 mg/m^2 of docetaxel on days 1, 8, and 15 of a 28-day cycle for three cycles. Patients with early evidence of disease progression before receiving all three cycles of vinorelbine were immediately sequenced to docetaxel. Treatment was limited to six total cycles of therapy. Treatment at the time of disease recurrence or progression after six cycles were left to the discretion of each treating physician.

LUN 6

Patients were randomized to receive 75 mg/m^2 of docetaxel intravenously on day 1 of a 21-day cycle or 30 mg/m^2 of docetaxel intravenously on days 1, 8, and 15 of a 28-day cycle. Treatment was continued until there was evidence of progressive disease or unacceptable side effects.

Response and Toxicity Criteria

Response and progression on both protocols were determined using the Response Evaluation Criteria in Solid Tumors criteria.[15] Adverse events were graded using the National Cancer Institute Common Toxicity Criteria 2.0.[16] Criteria for removal of patients from the study included completion of six cycles of chemotherapy (S0027), progression of disease or unacceptable toxicity as determined by the treating physician in consultation with the study coordinator, or patient refusal.

Statistical Considerations

S0027

The statistical design of S0027 has been outlined previously in the full study report.[13]

LUN 6

The primary objective of this trial was to assess the incidence of selected toxicities, with the hypothesis that the weekly schedule would be better tolerated. Assuming that 36% of patients on the schedule of every 3 weeks would experience at least one grade 3 or 4 toxicity, and assuming an 18% incidence rate of grade 3 or 4 toxicity for patients on the weekly schedule, a total of 106 patients for each treatment group would be needed to detect a treatment difference with 80% power at the 95% significance level.

RESULTS

Patient Characteristics

Between September 2001 and June 2003, 125 patients were registered for S0027. Of the 117 eligible patients, 23 were ages 80 years or older. Between August 2002 and February 2004, 111 patients were enrolled in the LUN 6 trial; 29 of these patients were ages 80 years or older. Three of the latter patients never received treatment, and the remaining 26 are considered in this analysis. Patient characteristics of the two 80-and-older subgroups from S0027 and LUN 6 are displayed in Table 1. Given the similarities between these two subpopulations in demographics, disease characteristics, and treatment (single-agent docetaxel or vinorelbine), for the

TABLE 1. Patient Characteristics

	LUN 6 (≥80)	S00 27 (≥80)	S00 27 (<80)
No. of patients	26	23	94
Males/females (%)	50/50	39/61	57/43
Stage IIIB/IV (%)	23/77	13/87	14/86
Performance status 0/1 or 2 (%)	80/20	70/30	64/36
Median age (yr)	81	82	73

purposes of this report the two 80-and-older groups were combined in reporting outcomes. In addition, the 94 patients from S0027 who were less than 80 years old were used as a comparative population to explore, in a preliminary fashion, relative outcomes between patients older than and younger than 80 years of age. Data on the under-80 group from the LUN 6 have not yet been updated and, therefore, are not included in this analysis. The characteristics of the under-80 population from S0027 are displayed in Table 1.

Treatment Received

Treatment was completed as planned (six cycles as coded by the data manager) in nine patients in the 80-and-older subgroup (39%) in S0027 compared with 43 patients in the under-80 group (46%). The median numbers of cycles received in the two groups were 4.5 and 5, respectively. For the 80-and-older subgroup, the exact number of cycles could not be determined in three patients, although they were known to have completed fewer than six. In the 80-and-older subgroup from LUN 6, the median numbers of cycles received on the every-3-weeks and weekly schedules were 4 (1–10) and 3 (1–8), respectively.

Toxicity

Treatment-related toxicity (grade 3 or higher), broken down by age and PS, is displayed in Table 2. In general, treatment was well tolerated. Grade 3 or 4 neutropenia was the most common toxicity, with 30% and 25% of patients ages 80 years or older with PS of 0/1 and 2, respectively, developing this adverse effect. In the under-80 group, grade 3/4 neutropenia was noted in 40% and 12% of patients with PS 0/1 and 2, respectively. Significant thrombocytopenia was rarely encountered in any patient population. Treatment-related deaths are listed in Table 3. Two patients (4%) who were 80 years or older, both of whom were in the every-3-weeks docetaxel arm of LUN 6, died from treatment-related adverse events. Three patients (3.2%) younger than 80 years also died from treatment-related adverse events.

Response and Survival

Objective responses to treatment for patients with measurable disease are displayed in Table 4. Disease control (partial response + stable disease) was obtained in 22 (59%) and 4 (36%) of patients ages 80 years or older with PS of 0/1 and 2, respectively. Disease control was seen in 29 (49%) and 12 (40%) of patients younger than 80 years old with PS of 0/1 and 2, respectively. Overall survival rates by age and PS are displayed in Figures 1 and 2. For patients with good PS (0 or 1), median and 1-year survival in the under-80 group were 11 months and 43%, respectively. In the 80-and-older group, median and 1-year survival were 7 months and 32%, respectively.

TABLE 2. Toxicity (Grade 3/4)

	Subgroups			
	≥80 PS 0–1 (*n* = 37) *n* (%)	**≥80 PS 2 (*n* = 12) *n* (%)**	**<80 PS 0–1[a] (*n* = 60) *n* (%)**	**<80 PS 2[a] (*n* = 34) *n* (%)**
Anemia	2 (5)	1 (8)	3 (5)	1 (3)
Neutropenia	11 (30)	3 (25)	24 (40)	4 (12)
Thrombocytopenia	1 (3)	0	0	0
Other (grade 2–4)	28 (76)	11 (92)	55 (92)	32 (94)
Any grade 5	1 (3)	1 (3)	1 (2)	2 (6)

[a] S0027 patients only.

TABLE 3. Treatment-Related Deaths

≥80 years old

86-year-old female, PS 1, q 3 week docetaxel, died of a cardiac arrest after 20 days on study

80-year-old M, PS 2, q 3 week docetaxel, died of sepsis after 17 days on study

<80 years old

71-year-old female, PS 1, died of infection without neutropenia after 104 days on study

72-year-old female, PS 2, died of respiratory failure after 12 days on study

72-year-old female, PS 2, died of respiratory failure after 26 days on study

PS, performance status.

TABLE 4. Responses among Patients with Measurable Disease

	Subgroups			
	≥80 PS 0–1 (*n* = 37) *n* (%)	**≥80 PS 2 (*n* = 11) *n* (%)**	**<80 PS 0–1[a] (*n* = 59) *n* (%)**	**<80 PS 2[a] (*n* = 30) *n* (%)**
Complete	0	0	0	0
Partial	3 (8)	1 (9)	13 (22)	3 (10)
Stable	19 (51)	3 (27)	16 (27)	9 (30)
Progression	8 (22)	4 (36)	18 (31)	11 (37)
Unevaluable	6 (16)	3 (27)	12 (20)	5 (17)
Early Death	1 (3)	0	0	2 (7)

PS, performance status.
[a] S0027 patients only.

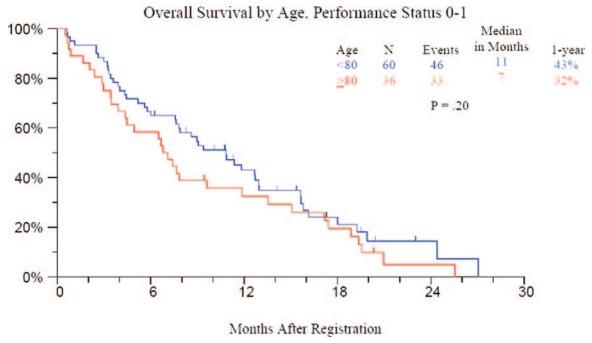

FIGURE 1. Overall survival by age, performance status 0 or 1.

DISCUSSION

The current demographics of lung cancer reflect the progressive aging of the general population in Western coun-

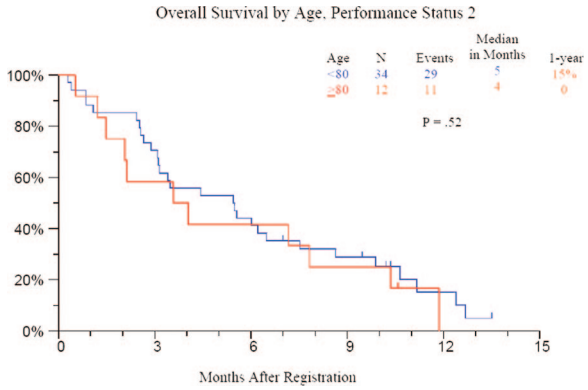

FIGURE 2. Overall survival by age, performance status 2.

tries. At present, two of every three patients diagnosed with lung cancer in the United States are older than 65 years of age, and at least one third of patients are ages 75 years or older.[2] Despite the preponderance of older patients with lung cancer, until recently, relatively little information was available from clinical trials to provide guidance on prognosis and appropriate management, particularly for patients with advanced-stage disease. For the 85% of patients with non-small cell subtypes of lung cancer, we know that the current standard of care for advanced disease is a platinum-based doublet.[17] In a subset of patients with certain clinical features, the addition of bevacizumab further improves outcome.[18]

To date, no prospective phase III trial evaluating the role of a platinum doublet has been conducted in a population of elderly patients with advanced NSCLC. Available data include analyses of elderly subsets from age-unspecified trials and some prospective studies assessing the role of single agents and nonplatinum combinations. The most commonly employed age for defining elderly patients in these trials is an age of 70 years or older. From the available data, a number of conclusions can be made about the treatment of patients ages 70 years or older with advanced NSCLC: (1) the value of single-agent therapy with drugs such as vinorelbine, gemcitabine, and docetaxel has been firmly established, (2) nonplatinum combinations are not clearly superior to single agents, and (3) the role of platinum-based doublets is not clearly defined; retrospective analyses would suggest that they are a reasonable option for the fit elderly.

It is unclear how applicable the available data on the use of chemotherapy in elderly patients with advanced NSCLC are for the "very old," who are defined as patients ages 80 years or older. Review of the literature reveals a near absence of data on the outcomes of chemotherapy for this group of patients. For example, in the landmark trial ECOG 1594, which evaluated four platinum-based doublets, nine patients (0.7%) out of the total of 1207 patients were ages 80 years or older.[19] Even on elderly-specific trials, patients ages 80 years or older have represented a small minority. In the three-arm Multicenter Italian Lung Cancer in the Elderly Study trial, the largest prospective elderly-specific trial conducted to date, patients ages 80 years or older constituted only 3.3% (23 patients) of the total of 698 evaluable patients.[12] Nevertheless, octenagarians constitute one of the most rapidly growing segments of the NSCLC population. More than 20% of the deaths from NSCLC will occur in patients ages 80 years or older.[1]

Given the paucity of data on treatment with chemotherapy in advanced NSCLC patients ages 80 years or older, we thought it might be instructive to review the outcomes in the combined 80-and-older cohorts from two recently conducted phase II trials. Both trials had similar eligibility targeting elderly and/or poor-PS patients, employed similar single-agent chemotherapy regimens, and had relatively high proportions of patients (21%; 49/233) ages 80 years or older with similar patient characteristics. We also have reported the results with the cohort of patients younger than 80 years old from one of the phase II trials (SWOG 0027), to allow an exploratory comparison between relative outcomes in the older and younger patients.

A number of conclusions can be drawn from this analysis. First, single-agent chemotherapy with either vinorelbine or docetaxel was relatively well tolerated. Grade 3 or 4 hematologic toxicities were the most common adverse events encountered, but these were rarely clinically significant, they were equally frequent in patients younger than 80 and in those 80 years and older, and treatment-related deaths were uncommon, ranging between 3% and 4% in both age groups. Secondly, patients with PS 2, regardless of age, fared equally poorly. Finally, patients ages 80 years or older with good PS had a relatively encouraging median survival of 7 months. This is comparable with the median survivals noted for the overall populations (>70 years) treated with single-agent chemotherapy in the three Italian elderly-specific trials; survival for those populations ranged between 4.2 and 8.3 months.[10–12] The only elderly-specific phase III trial reporting a higher median survival was the recent phase III trial comparing vinorelbine with docetaxel in patients ages 70 years or older, reported by the West Japan Thoracic Oncology Group.[20]

Despite the encouraging survival rate of the good-PS population ages 80 years or older, it is interesting to note that the survival of good-PS patients ages 70 to 79 years in the S0027 trial was still numerically better (11 months versus 7 months), raising the possibility that an age of 80 years or older may affect outcomes independently of PS.

Clearly, this analysis suffers from a number of potential shortcomings. As a retrospective, subset analysis, it is subject to all of the inherent limitations of such a review. In addition, it combines patient populations from two separate studies, with some variation in chemotherapy regimens and patient characteristics. Nevertheless, this report represents the largest reported experience to date on the outcomes with chemotherapy in a cohort of patients ages 80 years or older with advanced NSCLC. It allows one to hypothesize that selected patients ages 80 years or older with good PS might benefit from single-agent chemotherapy. This analysis provides a rationale for prospective trials of chemotherapy in patients ages 80 years or older with advanced NSCLC.

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